REMARKS

Claims 3-8, 10, 12, 15-17, 35-47, 55 and 57-63 are pending. Non-elected claims 5-8, 10, 12, 15-16, 35-47 and 55 were withdrawn from consideration by the Examiner.

The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. Support may be found, inter alia, at page 39, lines 10-13, and page 44, lines 10-14, of the specification. But if the Examiner should disagree, he is respectfully requested to point out the challenged limitation with particularity in the next Action so support may be cited in response.

The Examiner stated on page 2 of the Action, "The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98." No correction is necessary because the "listing" which the Examiner appears to be requesting is provided by the Form PTO-1449 that was filed with the Search Report and returned on June 20, 2005 with his initials. The information provided in the Search Report was provided for the Examiner's convenience.

Regarding the listings on Form PTO-1449 of the Int'l Search Report (see IDS of February 16, 2005) and the Int'l Preliminary Examination Report (see IDS of June 23, 2005), the Examiner is respectfully requested to consider that information and make it of record. In a telephone conversation with the Examiner, he alleged that such documents are not appropriate for listing on Form PTO-1449. Applicants disagree. No such limitation on the types of document which are listed is found in the United States Code, Code of Federal Regulations, or Manual of Patent Examining Procedure. Search reports are printed documents and acknowledgment that they were considered by printing them on the patent's face is appropriate. The Examiner is respectfully requested to provide legal authority in support of his allegation if he does not return initialed copies of the Form PTO-1449 submitted by Applicants on February 16, 2005 and June 23, 2005.

35 U.S.C. 112 – Definiteness

Claims 3-4, 17 and 57-63 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The Examiner objected to "sequence similarity" and suggested replacing it with "sequence identity" in amending the claims. But "sequence similarity" is a well-defined phrase in the art of sequence analysis. While sequence identity requires an exact match between sequences, sequence similarity allows substitutions of similar amino acids: i.e., aromatic Trp for aromatic Phe, positively charged Arg for positively charged Lys, etc. As a matter of fact, most common sequence alignment tools, such as the BLAST program from NCBI (http://www.ncbi.nlm.nih.gov/BLAST/) calculate relatedness in terms of sequence similarity. As similar substitutions are well within the ability of one of ordinary skill in the art (a search for "sequence similarity" in the PubMed database reveals that 9,392 publications used this term), Applicants urge that the subject claims particularly point out what Applicants regard as their invention. Furthermore, Applicants explicitly defined "sequence similarity" as "determined by comparing the amino acid sequence and its conservative amino acid substitutes." See, Applicants' specification at page 43, lines 23-25.

Favorable reconsideration is earnestly solicited.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 3-4, 17, 57 and 63 were rejected under Section 112, first paragraph, because it was alleged that the specification does not reasonably provide enablement for "isolated complexes comprising **derivatives of ubiquitin** with **fragments and derivatives of proteins** selected from the group consisting of aprataxin, SLP, HMG17, PinX1, CIR, HMGN3, HSPC144, tau, Cullin 3, and CDC6, formed via the N-end rule mechanism." He further alleged, "The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims." Applicants traverse.

A person skilled in the art would be able to practice the subject invention without undue experimentation in view of the disclosure in the specification and further in view of the high level of skill in the relevant art.

Applicants' specification clearly describes what they regard as fragments and derivatives (or variants) in claiming their invention.

> The variants of the polypeptides according to the present invention may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, (ii) one in which there are one or more modified amino acid residues, e.g., residues that are modified by the attachment of substituent groups, (iii) one in which the polypeptide is an alternative splice variant of the polypeptide of the present invention, (iv) fragments of the polypeptides and/or (iv) one in which the polypeptide is fused with another polypeptide, such as a leader or secretory sequence or a sequence which is employed for purification (for example, His-tag) or visualization (for example GFP). The fragments include polypeptides generated via proteolytic cleavage (including multi-site proteolysis) of an original sequence. Variants may be post-translationally, or chemically modified. Such variants are deemed to be within the scope of those skilled in the art from the teaching herein.

(specification at page 43, lines 9-22).

The specification describes the definition of the term "similarity" (see page 43, starting at line 23), what post-translational modifications can be used in the variants of the claimed proteins (see page 44, starting at line 15), and what unnatural amino acids can be used (see page 44, starting at line 25). The specification also teaches a skilled artisan, "The activity of these proteins as ubiquitylation substrates can be determined by measuring the accumulation of ubiquitylated products" (page 40, lines 11-13, and working examples on pages 76-89).

The "enablement" prong of the first paragraph of 35 U.S.C. 112 requires nothing more than objective enablement. Whether this is achieved by illustrative examples or by broad terminology is of no importance. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). Enablement is not precluded by the necessity for some experimentation such as routine

screening, but the experimentation needed to practice the invention must not be undue experimentation. The key word is undue, not experimentation. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, (Fed. Cir. 1988).

Applicants urge that the experimentation required to practice the full scope of the pending claims is reasonable and not undue, as a skilled artisan regularly engages in such experimentation.

With respect to the use of derivatives of ubiquitin, many ubiquitin derivatives have been prepared and been shown to have activity in ubiquitylation reactions. A person skilled in the art would, therefore, have a significant amount of information available to guide them in designing and predicting the activity of ubiquitin derivatives. See, e.g., the following references to ubiquitin derivatives:

(1) His6-ubiquitin is disclosed in http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&list_uids=8408016&dopt=Abstract;

(2) GST-ubiquitin is disclosed at http://www.cell.com/content/article/abstract?uid=PII0092867493903843;

(3) Biotin-ubiquitin is disclosed in Journal of Biomolecular Screening, 5(5):319-327 (2000);

(4) Fluorescently-labeled ubiquitin is disclosed in Journal of Protein Chemistry 19(6):489-498 (2000);

(5) Eu-ubiquitin (for a TR-FRET assay) is disclosed in Assay and Drug Development Technologies, 1(suppl. 2):175-180 (2003).

Applicants will gladly provide copies of all of the cited references to the Examiner, if he would like to review them in his evaluation of the claimed invention.

With respect to N-end rule ubiquitylation of protein fragments, Applicants' specification provides numerous examples of ubiquitylated protein fragments of the claimed proteins as characterized by gel electrophoresis (see pages 41-42, providing molecular weight and cleavage position estimates for characterized protein fragments, Examples 2-6, and corresponding gel electrophoresis images in Figures 3-7). Furthermore, the specification discloses a high-throughput screening method which will enable a skilled artisan to evaluate all variants and fragments of interest for the desired N-end rule

ubiquitylation. Screening multiple compounds using a well-developed assay is routine in the art.

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and M.P.E.P. § 2164.06,
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> The test for enablement is whether one reasonably skilled in the art to make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. A patent may be enabling even though some experimentation is necessary. *United States v. Telectronics, Inc.*) 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988).

Applicants urge that any experimentation that may be required would be routine in the art. Therefore, the pending claims are enabled by the disclosure in the specification. Although Applicants disagree with the basis of the Examiner's rejection, claims 3, 10, 17, 57 and 59 are amended to recite further technical features of the claimed invention. Favorable reconsideration is earnestly solicited.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 3-4, 17 and 57-63 were rejected under Section 112, first paragraph, because it was alleged that they contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse.

It appears from the Action that the Examiner contends that the specification does not clearly describe the derivatives of ubiquitin and/or the fragments or derivatives of a

protein. Applicants urge that the pending claims are clear in view of the disclosure in the specification and further in view of what is known in the art.

Applicants' specification discloses at page 32, "A person of ordinary skill in the art will recognize that the present invention relates not only to the specific protein sequences disclosed in the specification, but also to protein variants thereof such as fragments, analogs and/or derivatives." Moreover, the specification provides examples of what Applicants regard as protein variants on pages 43-45. And, furthermore, the specification provides methods for functionally testing the activity of these derivatives of ubiquitin and derivatives and fragments of proteins as ubiquitylation substrates by measuring the accumulation of ubiquitylated products (page 40, lines 11-13, and working examples on pages 76-89).

The pending claims require the complex between the protein and ubiquitin to be formed via a defined biological N-end rule pathway. This pathway imposes strict limits on the composition of matter and structurally restricts the final product (see specification at pages 4-5); in particular, the requirement for an exposed destabilizing N-terminal residue. Applicants urge that in view of the limitation requiring ubiquitylation via the N-end rule pathway, the claims exclude non-functional fragments and derivatives that are not substrates of the pathway, thereby reducing the breadth of claims.

Thus, the specification provides support for the presently claimed subject matter in compliance with the "written description" requirement of the first paragraph of 35 U.S.C. 112. The M.P.E.P. clearly states:

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116.
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> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). **Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas**

> **that show that the invention was complete, or by describing distinguishing identifying characteristics** sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct.304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

M.P.E.P. § 2163(I), emphasis added.

It is improper to reject claims on the basis that the specification does not support the claims when the terms of the claim are no broader than the broadest description of the invention in the specification and there is no reason to challenge the operativeness of the subject matter embraced by the claims. *Ex parte Altermatt*, 183 USPQ 436 (POBA 1974).

Although Applicants disagree with the basis of the Examiner's rejection, claims 3, 10, 17, 57 and 59 are amended to recite further technical features of the claimed invention. Favorable reconsideration is earnestly solicited.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

It appears that the Examiner potentially misinterprets the pending claims in the form of product-by process claims producing complexes identical to the products which are described in the cited references, but made via a different process. On the contrary, the complexes of the pending claims are chemically and structurally distinct from the products of the cited references. The pending claims require the complex between a specific protein and ubiquitin to be formed via a defined biological N-end rule pathway that targets proteins based on the presence of a destabilizing N-terminal amino acid.

(see specification at pages 4-5). Therefore, the claimed complexes comprise a protein that is ubiquitylated and also has a destabilizing N-terminal amino acid.

Claims 3-4 and 17 were rejected under Section 102(b) as allegedly anticipated by Kleinschmidt and Martinson (Nucl. Acids Res. 9:2423-2431, 1981; hereinafter "Kleinschmidt"). Applicants traverse.

Kleinschmidt describes a non-covalent complex between a ubiquitylated histone H2A and a non-ubiquitylated HMG17 and is thus clearly distinguished from the claimed product, namely an HMG17 covalently ubiquitylated via the N-end rule pathway.

Claims 57-59 and 62-63 were rejected under Section 102(b) as allegedly anticipated by Maeda et al. (FEBS Lett. 494:181-185, 2001; hereinafter "Maeda"). Applicants traverse.

Maeda also does not describe a product that falls within the scope of the claims. Maeda uses an N-terminal myc-Cullin fusion and detects the product by binding to the N-terminal myc sequence. The fact that the N-terminus of Maeda's myc-Cullin fusion is unaltered at the N-terminus is a clear indication that the protein was not processed to expose a destabilizing N-terminal residue and is, therefore, chemically and structurally different from the claimed product, namely Cullin ubiquitylated via N-end rule pathway.

Claims 57-59 and 62-63 were rejected under Section 102(b) as allegedly anticipated by Elsasser et al. (Mol. Biol. Cell 10:3263-3277, 1999; hereinafter "Elsasser"). Applicants traverse.

Similarly, Elsasser discloses five deletion mutants (Δ8-46, Δ3-16, Δ13-26, Δ23-36, Δ33-46) (see page 3269, Figure 2), all of which preserve the N-terminal amino acid. This is a clear indication that Elsasser's product is chemically and structurally different from the claimed product because Elsasser's substrate was not processed to expose a destabilizing N-terminal residue.

Claims 57-59 and 62-63 were rejected under Section 102(b) as allegedly anticipated by Morishima-Kawashima et al. (Neuron 10:1151-1160, 1993; hereinafter "Morishima-Kawashima"). Applicants traverse.

Finally, Morishima-Kawashima teaches that out of six ubiquitylated sequences, four start with glutamic acid (Glu, E), one starts with valine (Val, V) and one starts with

serine (Ser, S) (see page 1155, Table 1) – none of which is a destabilizing N-terminal residue required for N-end rule ubiquitylation. This is a clear indication that Morishima-Kawashima's product is chemically and structurally different from the claimed product.

Consequently, the product-by process analysis applied by the Examiner is misleading because the pending claims are directed to chemically and structurally distinct products. Favorable reconsideration is earnestly solicited.

Conclusion

In view of the above, Applicants submit that the claims are in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Moreover, due to the large number of issues which were present in responding to this Office Action, Applicants believe that an interview would be helpful in addressing any issues which were not successfully traversed in this response or overcome by this response. Thus, Applicants respectfully request an interview with the Examiner once this response has been reviewed.

Respectfully submitted,

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